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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

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☐ Additional inventors are being named on the separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

COMPOSITIONS FOR REDUCING INFLAMMATION AND USES THEREOF

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages 17 ☐ Small Entity Statement

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METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

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☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE _____ Date March 1, 2004

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COMPOSITIONS FOR REDUCING INFLAMMATION AND USES THEREOF

BACKGROUND OF THE INVENTION

(a) Field of the Invention

[0001] This invention relates to new compositions for reducing and/or treating inflammation and/or pro-inflammatory condition and uses thereof.

(b) Description of Prior Art

[0002] Cystic Fibrosis (CF) is the most common lethal hereditary disease among Caucasians and it is characterized by a biochemical abnormality in CFTR (cystic fibrosis transmembrane conductance regulator) channel. The most common clinical manifestation in CF is chronic lung infection that leads to progressive tissue destruction and elevated pulmonary morbidity and mortality. Lung tissue damage in cystic fibrosis has been related to an abnormally exacerbated immune response in CF cells. This exacerbation has been related to an exaggerated activation of the pro-inflammatory transcriptional factor NF-kB.

[0003] One molecule that is known to inhibit NF-kB activation is ceramide, a sphingolipid recognized as a second messenger in the molecular modulation of apoptosis. The sphingomyelin (SM) cycle, with the conversion of SM to ceramide by sphingomyelinase (SMase), is a key signaling pathway in many cell systems. Two main routes have been defined for the generation of ceramide: (1) hydrolysis of SM, an abundant sphingolipid species in cell membranes, by the action of SMases; and (2) by *de novo* biosynthesis catalyzed by ceramide synthase. The hydrolytic pathway, however, is the major source for ceramide in cellular responses to extracellular signaling (i.e., tumor necrosis factor alpha, lipopolysaccharides, gamma-interferon, and interleukins).

[0004] Cellular treatment with TNF-α has emerged as one of the best-characterized models of cytokine-induction and of ceramide function. TNF-α induces activation of SMase in these cells and this activation is a consequence of the drop of GSH that follows the activation of the death receptor and caspase 8. Conversely, extracellular supplementation of

GSH or N-acetylcysteine (NAC), a known precursor of GSH inhibit ceramide generation induced via oxidative stressors such as TNF-α, interleukin-1-β, hypoxia, and doxorubicin. GSH inhibits the activation of the neutral, magnesium-dependent SMase and inhibits ceramide generation induced by TNF-α in human mammary carcinoma cells. In addition, it has been shown that low GSH levels in lung cells were required for ceramide production, whereas high GSH levels inhibit the generation of ceramide.

[0005] GSH concentrations have been suggested to be relatively high in cystic fibrosis lung epithelial cells have recently shown that CFTR deficient cells are less sensitive to oxidative stress induced by H_2O_2 than normal cells (Jungas T. *et al.*, 2002 *J Biol Chem.* **277**:27912-8.). These authors suggested that the resistance to oxidative stress is in part due to inherently high constitutive GSH levels in the CFTR-deficient cells. Moreover, fenretinide has been shown to increase endothelial ceramide by *de novo*, non-sphingomyelinase-mediated ceramide synthesis (Erdreich-Epstein, A. *et al.*, 2002 *J Biol Chem*, **277**, 49531-49537). Fenretinide is an active, less toxic synthetic amide of all-trans-retinoic acid (RA) that has been well tolerated in phase I trials in humans. *In vitro* studies have demonstrated that fenretinide induces apoptosis in several tumor cell types including ovarian, breast and gliomal tumor cells. It is used orally as a chemopreventive against prostate cancer and in pre-menopausal women at risk of developing ovarian and contralateral breast cancers.

[0006] It would be highly desirable to be provided with new compositions for reducing and/or treating inflammation and/or proinflammatory condition particularly in patients suffering from lung conditions, such as cystic fibrosis.

SUMMARY OF THE INVENTION

[0007] One aim of the present invention is to provide new compositions for reducing and/or treating inflammation and/or pro-inflammatory condition in patients suffering from such conditions.

[0008] In accordance with the present invention there is provided a composition for reducing and/or treating inflammation in a patient, comprising an effective amount of ceramide in association with a pharmaceutically acceptable carrier.

[0009] In a preferred embodiment of the present invention, the ceramide is present in a concentration varying from 0.1 to 10μM (plasma concentration), preferably 1μM.

[0010] In a preferred embodiment of the present invention, the composition is for administration via a route selected from the group consisting of oral, intravenous, parenteral, intramuscular, topical, subcutaneous, intranasal and anal route.

[0011] In one embodiment of the present invention, the composition of the present invention further comprises an agent for inducing ceramide production in the patient.

[0012] In accordance with the present invention, there is provided a composition for reducing and/or treating inflammation in a patient, comprising an effective amount of an agent for inducing ceramide production in the patient in association with a pharmaceutically acceptable carrier.

[0013] In a preferred embodiment of the present invention, the composition for reducing and/or treating inflammation comprising an agent for inducing ceramide production comprises this agent in a concentration varying from 0.1 to 12.9μM, preferably a concentration of 3μM.

[0014] In one embodiment of the present invention, the composition further comprises an effective amount of ceramide.

[0015] In accordance with the present invention, there is provided a composition for reducing and/or treating pro-inflammatory condition in a patient, comprising an effective amount of ceramide in association with a pharmaceutically acceptable carrier.

[0016] Preferably, the ceramide is present in a concentration varying from 0.1 to 10μM (plasma concentration), more preferably in a concentration of 1μM.

[0017] In one embodiment of the present invention, the composition further comprises an agent for inducing ceramide production in the patient.

[0018] In accordance with the present invention, there is provided a composition for reducing and/or treating pro-inflammatory condition in a

patient, comprising an effective amount of an agent for inducing ceramide production in the patient in association with a pharmaceutically acceptable carrier.

[0019] Preferably the agent is present in a concentration varying from 0.1 to 12.9μM, more preferably in a concentration of 3μM.

[0020] In one embodiment of the present invention, the composition further comprises an effective amount of ceramide.

[0021] In accordance with the present invention, there is provided a composition for reducing and/or treating inflammation in a patient, comprising an effective amount of fenretinide in association with a pharmaceutically acceptable carrier.

[0022] In accordance with the present invention, there is provided a composition for reducing and/or treating pro-inflammatory condition in a patient, comprising an effective amount of fenretinide in association with a pharmaceutically acceptable carrier.

[0023] In accordance with the present invention, there is provided a method for reducing and/or treating inflammation in a patient, this method comprising the step of administering an effective amount of the composition of the present invention to the patient.

[0024] In accordance with the present invention, there is provided the use of the composition of the present invention for reducing and/or treating inflammation in a patient.

[0025] In accordance with the present invention, there is provided the use of the composition of the present invention for the preparation of a medicament of reducing and/or treating inflammation in a patient.

[0026] In accordance with the present invention, there is provided a method for reducing and/or treating pro-inflammatory condition in a patient, the method comprising the step of administering an effective amount of the composition of the present invention to the patient.

[0027] In accordance with the present invention, there is provided the use of the composition of the present invention for reducing and/or treating pro-inflammatory condition in a patient.

[0028] In accordance with the present invention, there is provided the use of the composition of the present invention for the preparation of a medicament of reducing and/or treating pro-inflammatory condition in a patient.

[0029] The inflammation in the patient is caused by a lung disease such as cystic fibrosis or an immune related disease such as, but not limited to, allergic asthma, rheumatoid arthritis, multiple sclerosis, diabetes and inflammatory bowel disease.

[0030] In the present invention, the compositions are suitable for administration via a route selected from the group consisting of oral, intravenous, parenteral, intramuscular, topical, subcutaneous, intranasal and anal route.

[0031] Cystic Fibrosis (CF) is characterized by a biochemical abnormality in CFTR (cystic fibrosis transmembrane conductance regulator) channel. CFTR-deficient lung epithelial cells demonstrate a pro-inflammatory immune hyper-responsiveness ascribed to an exaggerated activation of the pro-inflammatory transcriptional factor NF-kB. CFTR-deficient cells also have been indicated to have an inherently high constitutive GSH level which inhibit the generation of ceramide in CF cells. As ceramide inhibits NF-kB activation, supplementation of ceramide or ceramide up-regulating drugs decreases the pro-inflammatory state in CF. Normal and CFTR deficient human bronchial epithelial cells (16HBE14o-, and CBFE41o- with delta F508 CFTR mutation respectively) were treated with C6-ceramide (1 μM) or a pharmacological inducer of cellular ceramide, fenretinide (2.5 and 5 μM). The output of IL-8 was determined as an indicator of cellular immune response. Both fenretinide doses and the ceramide treatment were associated with decreased IL-8 release in CFTR deficient cells in the non-inflamed state. Normal cells in non-inflammatory conditions had decreased IL-8 release (47.3%) for the lower fenretinide dose but a stimulatory effect for the higher dose (19.8%). When the pro-inflammatory agent TNF-α was added to the cell cultures, normal cells increased IL-8 production by 63% whereas the CFTR deficient cells showed a 165% increase in IL-8 release. Ceramide pre-treatment was associated with decreased IL-8 release (12.9%) in normal cells exposed to

TNF-α whereas CFTR deficient cells demonstrated no protection. When cells were pre-treated with fenretinide (2.5 μM), an inhibition in IL-8 release in the TNF-α treated CFTR-deficient (33.6%) and normal (17.5%) cells was observed.

[0032] For the purpose of the present invention the following terms are defined below.

[0033] The term "pro-inflammatory condition" is intended to mean a chronic inappropriate proliferation of pathogenic cells in a target tissue followed by inflammatory reaction. An infection is not required to initiate the chronic inflammatory response by subsequent infection can exacerbate tissue damage. Such condition is present in diseases such as, but not limited to, cystic fibrosis, rheumatoid arthritis, multiple sclerosis, diabetes, inflammatory bowel disease and allergic asthma.

[0034] The term " agent for inducing ceramide production" is intended to mean an agent, such as, but not limited to, fenretinide which induces ceramide production in a subject when administered.

[0035] All references herein are hereby incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] Fig. 1 illustrates the effect of ceramide and fenretinide on IL-8 release by normal bronchial epithelial cells in non-inflammatory conditions;

[0037] Fig. 2 illustrates the effect of ceramide and fenretinide on IL-8 release by CFTR-deficient bronchial lung epithelial cells in non-inflammatory conditions;

[0038] Fig. 3 illustrates the effect of ceramide and fenretinide on IL-8 release by normal bronchial epithelial cells in inflammatory conditions; and

[0039] Fig. 4 illustrates the effect of ceramide and fenretinide on IL-8 release by CFTR-deficient bronchial lung epithelial cells in inflammatory conditions.

DETAILED DESCRIPTION OF THE INVENTION

[0040] In accordance with the present invention, there is provided compositions comprising an effective amount of ceramide for reducing and/or treating inflammation and/or pro-inflammatory condition as well as

compositions comprising an agent for inducing ceramide production when administered to this patient. There is also provided compositions comprising fenretinide for reducing and/or treating inflammation and/or pro-inflammatory conditions.

Materials and Methods

Materials

[0041] Normal and CFTR deficient human bronchial epithelial cells (16HBE14o-, and CBFE41o- with delta F508 CFTR mutation respectively) were a gift obtained from Dr. D. Gruenert (University of California). The supplies for the maintenance of cell culture such as minimum essential medium, fetal bovine serum, penicillin- streptomycin, L- glutamine, and Dulbecco's phosphate-buffered saline were obtained from Gibco BRL. Trypsin-EDTA solution (0.25%) was obtained from Sigma-Aldrich Co. The solution used to coat the T-75 flasks and 24-well plates was prepared with collagen type I bovine, and human fibronectin obtained from BD Biosciences; and EGTA, BSA, and LHC basal medium obtained from Biofluids Biosource. Human recombinant TNF-α was obtained from BD Pharmigen and prepared with BSA 0.1%. To determine IL-8 release ELISA kits (Pharmigen, OptEIA Human IL-8 Set) were obtained from BD Bioscience. Cell viability was determining by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) obtained from Sigma-Aldrich Co. Retinamide N-(4-hydroxyphenyl)-retinamide and Ceramide C6 (N-hexanoyl-d-sphingosine) were obtained from Sigma-Aldrich Co.

Cells culture

General procedures

[0042] Normal (16HBE14o-) and CFTR deficient human epithelial cells (CBFE41o- with delta F508 CFTR mutation) were grown in pre-coated T - 75 flasks in a medium containing (10% FBS), re-fed every 2-3 days until confluence when they were split to 24-well plates for about 24 hours before receiving the treatments.

Treatment with fenretinide, ceramide and TNF-α

[0043] Normal and CFTR deficient cells were treated with fenretinide and C6-ceramide at doses established previously in cell culture studies to

effectively increase cellular ceramide content. Normal (16HBE14o-) and CFTR deficient human epithelial cells (CBFE41o-), 0.4 and 0.5 x 10^6/well in 24-well plates, were incubated with 2.5 µM or 5 µM of fenretinide and 1uM of ceramide for 24 h in a minimum essential medium (MEM) containing 10% FBS. After 24h, the medium was replaced by MEM 2% FBS and the cells were incubated with the same concentrations of fenretinide or ceramide to characterize non inflammatory condition. To characterize inflammatory condition the cells were treated with fenretinide or ceramide and concurrently stimulated with human recombinant TNF-α for more 24h.

IL-8 release and cell viability assays

[0044] After the treatment described above, the supernatant was collected to determine IL-8 released using an ELISA kit (Pharmigen, OptEIA Human IL-8 Set) and following the company instructions. Briefly, 96-well plates were coated with capture antibody overnight, washed with PBS, 0.05% Tween-20™ and coated with PBS, 10% heat-inactivated FBS. Known concentrations of TNF-α (standard) and the samples containing the TNF-α released by the cells after treatment (supernatant) were added as aliquots into appropriate wells, incubated for 2h and decanted from the wells. Anti-IL-8 plus enzyme reagent were added and incubated for 1 h. After washing the plate, a solution was added which contained a substrate for the enzyme present in the anti-IL-8 + enzyme reagent mixture and the plate was incubated for 30 min. The reaction was stopped using a 2N H_2SO_4 solution and the absorbance was read at 450nm.

[0045] The cell viability was assessed using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Briefly, after collecting the supernatant to determine IL-8 release, the cells were gently washed with PBS, MTT solution (MTT, 0.5mg/mL culture medium free of phenol red) was added and the cells were incubated for 4 hours at 37°C. After incubation, the supernatant was aspirated, HCl-isopropanol solution (0.04N HCl in isopropanol) was added and after 5 minutes the optical densities were measured at 540nm. The test is based upon formation of a blue formazan product, due to reduction of the yellow MTT tetrazolium salt by mitochondrial reductases, which belongs to the respiratory chain and is

active only in metabolically active cells. The intensity of color reaction correlates with cell number and metabolic activity of the cells. In cells with equal activity, the test can be used to determine the percentage of viable cells.

Results and Discussion

[0046] In Fig. 1, normal human epithelial cells (16HBE14o-), were plated at a concentration of $0.4x10^6$/well in a 24-well plate. After confluence. the cells were incubated with 2.5µM or 5µM of fenretinide (4-HPR) and with 1µM of ceramide for 24 hours in a minimum essential medium (MEM) containing 10% FBS. After 24h, the medium was replaced by MEM 2% FBS and the cells were incubated with the same concentrations of 4-HPR and ceramide for more 24 hours. The IL-8 content in the supernatant was collected to determine IL-8 release using an ELISA kit (Pharmigen, OptEIA Human IL-8 set) and cell viability was assessed using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. In Fig. 2, the same procedure was applied to CFTR deficient human epithelial cells (CBFE41o- with delta F508 CFTR mutation), $0.25x10^6$/well in a 24-well plate. Bars represent the percentage of IL-8 released adjusted to cell viability. Taking into consideration the cell viability, both fenretinide (2.5 and 5µM) and ceramide (1µM) decreased IL-8 release in CFTR deficient cells in non-inflammatory conditions (Fig. 2) The inhibition was similar for both the lower (56.7%) and higher (50%) doses of fenretinide. Normal cells had decreased IL-8 release for the lower dose (47.3%) but a stimulatory effect for the higher doses (19.8%) was observed (Fig. 1). The low dose of ceramide promoted a decrease in IL-8 release in CFTR deficient and normal cells of 43.2% and 21.7% respectively (Figs. 1 and 2). These results show that inflammation in CF can be minimized via exposure to fenretidine and ceramide.

[0047] When the pro-inflammatory agent TNF-α was added to the cell cultures, normal cells increased IL-8 production by 63% and 84% (Fig. 3) whereas the CFTR deficient cells showed a 265% and 248% increase in IL-8 release (Fig. 4). The exacerbated response to TNF-α was expected for CFTR deficient cells as previously mentioned; however, when cells were pre-treated with fenritinide (2.5µM), an inhibition in IL-8 release in

CFTR-deficient (33.6%) and normal (17.5%) cells was observed (Figs. 3 and 4). The unexpected observation that fenretinide also reduced IL-8 release in normal epithelial lung cells shows that fenretinide acts as an anti-inflammatory agent. It is also shown that fenretinide act to attenuate inflammation in the pro-inflammatory state.

[0048] More than 1500 retinoids have been tested so far but very few of them have been entered into clinical trials because of their side-effects. Fenretinide is a synthetic retinoid that is reported to have fewer side-effects compared to naturally occurring retinoids including vitamin A (Ulukaya, E. and Wood, E.J., 1999, *Cancer Treat Rev.* **25**: 229-35). The safety profile for fenretinide is excellent as minimal side-effects have been noted in a variety of clinical trials using fenretinide on a prophylactic basis (Ulukaya, E. and Wood, E.J., 1999, *Cancer Treat Rev.* **25**: 229-35). Clinical trials have shown that fenretinide does not induce generalized vascular damage in humans (Reynolds, C.P. and Lemons R.S., 2001, *Hematol Oncol Clin North Am.* **15**: 867-910). Fenretinide has also been used to treat subjects (aged 2-21 yr.) with neuroblastoma: (a) to define fenretinide pharmacokinetics and maximal tolerated dose in children and (b) to assess short- and mid-term toxicity in this age range (Garaventa, A., *et al.*, 2003, *Clin. Cancer Res.* **9**: 2032-2039). Fenretinide was given orally once a day in 28-day courses. Liver and renal functions and clinical evaluation were assessed weekly. The side effects that occurred in 15 of the tested 45 subjects were the same as those observed in adult subjects. The side effects were noted to be tolerable and readily reversible within 7 days following discontinuation of the treatment.

[0049] The above data has demonstrated preliminary evidence that pre-treatment with ceramide up-regulating drugs could be advantageous for lung inflammation in CF. The use of fenretinide in this regard is particularly exciting due to its low systemic toxicity as this drug has been used on a prophylactic basis to decrease cancer risk in the general population. Hence, this drug is a strong candidate as a potential primary treatment to ameliorate chronic and acute lung inflammation in CF, which is a primary cause of mortality and morbidity in CF.

[0050] The unexpected observation that fenretinide also reduced IL-8 release in normal eptithelial lung cells shows that fenretinide also serve as an anti-inflammatory agent in other medical conditions, such as, but not limited to, rheumatoid arthritis, multiple sclerosis, diabetes, inflammatory bowel disease and allergic asthma.

[0051] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. A composition for reducing and/or treating inflammation in a patient, comprising an effective amount of ceramide in association with a pharmaceutically acceptable carrier.

2. The composition of claim 1, wherein said inflammation is lung inflammation.

3. The composition of claim 1, wherein said inflammation is caused by a disease selected from the group consisting of cystic fibrosis, allergic asthma, rheumatoid arthritis, multiple sclerosis, diabetes and inflammatory bowel disease.

4. The composition of claim 1, wherein said ceramide is present in a concentration varying from 0.1 to 10μM (plasma concentration).

5. The composition of claim 1, wherein said ceramide is present in a concentration of 1μM (plasma concentration).

6. The composition of claim 1, wherein said composition is for administration via a route selected from the group consisting of oral, intravenous, parenteral, intramuscular, topical, subcutaneous, intranasal and anal route.

7. The composition of claim 1, further comprising an agent for inducing ceramide production in said patient.

8. The composition of claim 7, wherein said agent is selected from the group consisting of fenretinide and synthetic retinoids.

9. A composition for reducing and/or treating inflammation in a patient, comprising an effective amount of an agent for inducing ceramide production in said patient in association with a pharmaceutically acceptable carrier.

10. The composition of claim 9, wherein said inflammation is lung inflammation.

11. The composition of claim 9, wherein said agent is selected from the group consisting of fenretinide and synthetic retinoids.

12. The composition of claim 9, wherein said inflammation is caused by a disease selected from the group consisting of cystic fibrosis, allergic asthma, rheumatoid arthritis, multiple sclerosis, diabetes and inflammatory bowel disease.

13. The composition of claim 9, wherein said agent is present in a concentration varying from 0.1 to 12.9μM.

14. The composition of claim 9, wherein said agent is present in a concentration of 3μM.

15. The composition of claim 9, wherein said composition is for administration via a route selected from the group consisting of oral, intravenous, parenteral, intramuscular, topical, subcutaneous, intranasal and anal route.

16. The composition of claim 9, further comprising an effective amount of ceramide.

17. A method for reducing and/or treating inflammation in a patient, said method comprising the step of administering an effective amount of the composition of any one of claims 1 to 16 to said patient.

18. Use of the composition of any one of claims 1 to 16 for reducing and/or treating inflammation in a patient.

19. Use of the composition of any one of claims 1 to 16 for the preparation of a medicament of reducing and/or treating inflammation in a patient.

20. A composition for reducing and/or treating pro-inflammatory condition in a patient, comprising an effective amount of ceramide in association with a pharmaceutically acceptable carrier.

21. The composition of claim 20, wherein said pro-inflammatory condition is selected from the group consisting of cystic fibrosis, allergic asthma, rheumatoid arthritis, multiple sclerosis, diabetes and inflammatory bowel disease

22. The composition of claim 20, wherein said ceramide is present in a concentration varying from 0.1 to 10μM (plasma concentration).

23. The composition of claim 20, wherein said ceramide is present in a concentration of 1μM.

24. The composition of claim 20, wherein said composition is for administration via a route selected from the group consisting of oral, intravenous, parenteral, intramuscular, topical, subcutaneous, intranasal and anal route.

25. The composition of claim 20, further comprising an agent for inducing ceramide production in said patient.

26. The composition of claim 25, wherein said agent is selected from the group consisting of fenretinide and synthetic retinoids.

27. A composition for reducing and/or treating pro-inflammatory condition in a patient, comprising an effective amount of an agent for inducing ceramide production in said patient in association with a pharmaceutically acceptable carrier.

28. The composition of claim 27, wherein said agent is selected from the group consisting of fenretinide and synthetic retinoids.

29. The composition of claim 27, wherein said pro-inflammatory condition is selected from the group consisting of cystic fibrosis, allergic asthma, rheumatoid arthritis, multiple sclerosis, diabetes and inflammatory bowel disease.

30. The composition of claim 27, wherein said agent is present in a concentration varying from 0.1 to 12.9μM.

31. The composition of claim 27, wherein said agent is present in a concentration of 3μM.

32. The composition of claim 27, wherein said composition is for administration via a route selected from the group consisting of oral, intravenous, parenteral, intramuscular, topical, subcutaneous, intranasal and anal route.

33. The composition of claim 27, further comprising an effective amount of ceramide.

34. A method for reducing and/or treating pro-inflammatory condition in a patient, said method comprising the step of administering an effective amount of the composition of any one of claims 20 to 33 to said patient.

35. Use of the composition of any one of claims 20 to 33 for reducing and/or treating pro-inflammatory condition in a patient.

36. Use of the composition of any one of claims 20 to 33 for the preparation of a medicament of reducing and/or treating pro-inflammatory condition in a patient.

37. A composition for reducing and/or treating inflammation in a patient, comprising an effective amount of fenretinide in association with a pharmaceutically acceptable carrier.

38. The composition of claim 37, wherein said inflammation is lung inflammation.

39. The composition of claim 37, wherein said inflammation is caused by a disease selected from the group consisting of cystic fibrosis, allergic asthma, rheumatoid arthritis, multiple sclerosis, diabetes and inflammatory bowel disease.

40. The composition of claim 37, wherein said fenretinide is present in a concentration varying from 0.1 to 10μM.

41. The composition of claim 37, wherein said fenretinide is present in a concentration of 1μM.

42. The composition of claim 37, wherein said composition is for administration via a route selected from the group consisting of oral, intravenous, parenteral, intramuscular, topical, subcutaneous, intranasal and anal route.

43. A method for reducing and/or treating inflammation in a patient, said method comprising the step of administering an effective amount of the composition of any one of claims 37 to 42.

44. Use of the composition of any one of claims 37 to 42 for reducing and/or treating inflammation in a patient.

45. Use of the composition of any one of claims 37 to 42 for the preparation of a medicament of reducing and/or treating inflammation in a patient.

46. A composition for reducing and/or treating pro-inflammatory condition in a patient, comprising an effective amount of fenretinide in association with a pharmaceutically acceptable carrier.

47. The composition of claim 46, wherein said pro-inflammatory condition is selected from the group consisting of cystic fibrosis, allergic asthma, rheumatoid arthritis, multiple sclerosis, diabetes and inflammatory bowel disease.

48. The composition of claim 46, wherein said agent is present in a concentration varying from 0.1 to 12.9μM.

49. The composition of claim 46, wherein said agent is present in a concentration of 3μM.

50. The composition of claim 46, wherein said composition is for administration via a route selected from the group consisting of oral, intravenous, parenteral, intramuscular, topical, subcutaneous, intranasal and anal route.

51. A method for reducing and/or treating pro-inflammatory condition in a patient, said method comprising the step of administering an effective amount of the composition of any one of claims 46 to 50 to said patient.

52. Use of the composition of any one of claims 46 to 50 for reducing and/or treating pro-inflammatory condition in a patient.

53. Use of the composition of any one of claims 46 to 50 for the preparation of a medicament of reducing and/or treating pro-inflammatory condition in a patient.

ABSTRACT OF THE INVENTION

The present invention relates to compositions for reducing and/or treating inflammation in a patient and compositions for reducing and/or treating pro-inflammatory condition in a patient, comprising an effective amount of ceramide in association with a pharmaceutically acceptable carrier. The present invention relates also to compositions for reducing and/or treating inflammation in a patient and compositions for reducing and/or treating pro-inflammatory condition in a patient, comprising an effective amount of an agent inducing ceramide production in association with a pharmaceutically acceptable carrier. The present invention further relates to compositions for reducing and/or treating inflammation in a patient and compositions for reducing and/or treating pro-inflammatory condition in a patient, comprising an effective amount of fenretinide in association with a pharmaceutically acceptable carrier.

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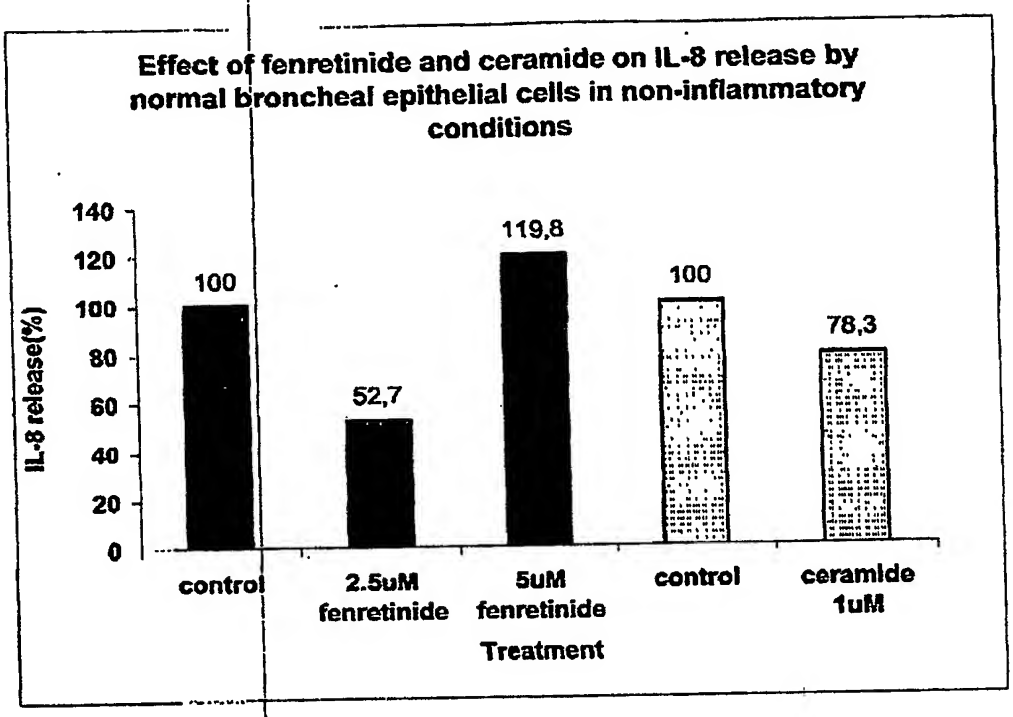

Fig. 1

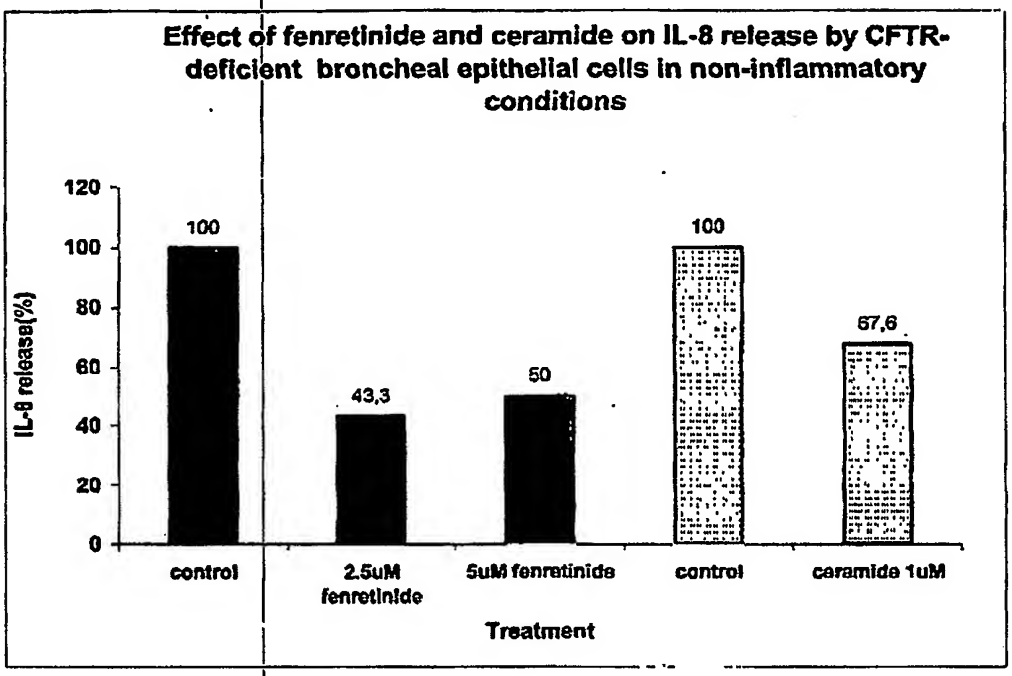

Fig. 2

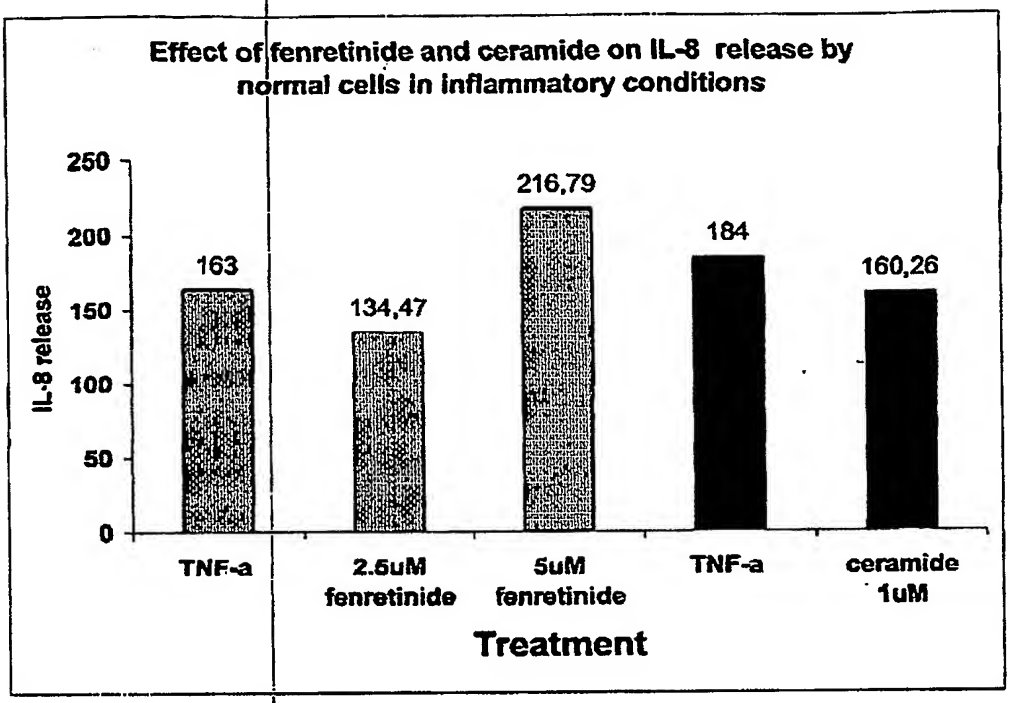

Fig. 3

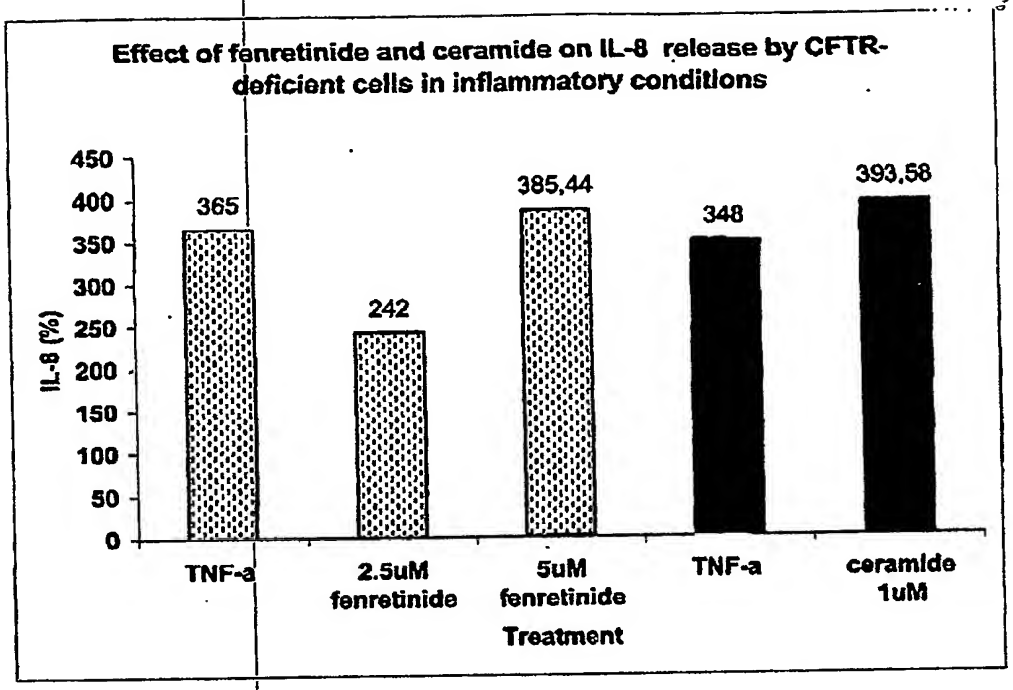

Fig. 4